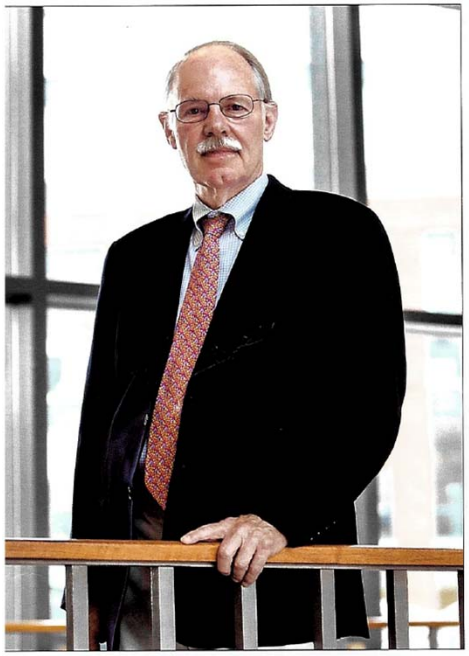
State of D2d

ANASTASSIOS G. PITTAS, MD, MS

ON BEHALF OF THE D2d RESEARCH GROUP

IN MEMORIAM

JAMES H. WARE



James H. Ware, the Frederick Mosteller Professor of Biostatistics and associate dean for clinical and translational science, passed away April 26 after a long battle with cancer.

Ware was a deeply respected and admired member of the Harvard Chan School community for nearly 40 years. Colleagues described him as a brilliant statistician, a committed mentor to students, and a truly caring person whose words "always came with a smile." As acting dean between Deans Harvey V. Fineberg and Barry R. Bloom, Ware played a significant role in shaping the School's academic and research vision—a legacy upon which the School of today is built.

Ware joined the faculty in 1979 after receiving his PhD in statistics from Stanford University and spending eight years as a mathematical statistician at the National Heart, Lung, and Blood Institute. He was dean for academic affairs at the School from 1990 to 2009, including serving as acting dean of the faculty from 1997 to 1998. Ware taught clinical trials research methods for many years at the School and was involved in the development of master's degree programs in epidemiology and biostatistics with international partners in Cyprus and Saudi Arabia.

Ware had a long-standing interest in studies of pulmonary and cardiovascular disease. From 1980 to 1995, he was a co-investigator in the landmark Six Cities Study of Air Pollution and Health, which had a profound effect on Clean Air Act of 1970 regulations in the U.S. and on efforts to limit air pollution around the world.

Ware was internationally recognized for his publications on the design and analysis of longitudinal and multilevel physiological, clinical, and biological studies and on methodological issues in clinical trials research. He was senior statistician for randomized trials of strategies for protecting the brain during surgical repair of transposition of the great arteries in infants, chelation therapy for lead-exposed children, and, more recently, research examining vitamin D supplementation to prevent development of diabetes and the role of sleep apnea in diabetes.

Jim Ware

Frederick Mosteller Professor of Biostatistics & Associate Dean for Clinical and Translational Science

During his remarkable career of more than 45 years, Jim Ware's work in academic affairs, teaching, and scholarship was marked by an unwavering dedication to his profession, his colleagues, and the institutions he served.

He was an extremely popular and inspirational teacher, with a unique ability to communicate complex ideas in a straightforward manner to a diverse audience. Extremely thoughtful and judicious in his leadership roles, he enabled projects to thrive and flourish.

Jim was the embodiment of what we all hope for in a colleague and mentor – generous with his time, eternally optimistic, enthusiastic, supportive, and kind.

Meet our new D2d team members

Name	Site	Site Role
Saif Almushhadani	MedStar (Baltimore)	Research Coordinator
Marina Perez, LIC	LA	Research Phlebotomist
Omar Khalid	MedStar (Hyattsville)	Research Coordinator
Kellie Gervas	Duke	Research Assistant
Julie Costello	Atlanta	Research Coordinator
Sakina Kazmi	Northwestern	Research Coordinator
Tara Asgarpoor	Nebraska (Omaha VA)	Research Assistant
Karina Ziskovich, BBA	Lenox Hill	Research Coordinator
Mahmoud Hassan, MD, MPH	Lenox Hill	Project Manager
Blair Martin	Cleveland	Research Coordinator
Lisa Ceglia, MD	Tufts	Site PI
Dave Reboussin, Ph.D		Lead Statistician

Colt [Nebraska]

Son of Jeff Newcomb

Nolan [Baltimore]

Son of Theresa Young

Ada [MUSC]

Daughter of Suzanne Kuker

From: Kuker, Suzanne [mailto:kuker@musc.edu]
Sent: Wednesday, April 06, 2016 9:39 AM
To: Vickery, Ellen
Subject: Re: tomorrow's call

I'm actually in labor. :) Please call Mary at 843-792-5428 to schedule a time for her and Rhoda. Thanks.

Sent from my iPhone

On Apr 6, 2016, at 8:43 AM, Vickery, Ellen <evickery@tuftsmedicalcenter.org> wrote:

> Hi Suzanne,
>
> That's fine. Why don't you plan to call me around 1pm – does that sound good?
>
> Ellen

Dexter [NW]

Son of Jenny Lewandowski

Olivia [Tufts]

Daughter of Kim Vo

Importance and Relevance of D2d

IS D2d STILL RELEVANT?

Implications of recent literature on vitamin D and type 2 diabetes for D2d

JORDE ET AL. VITAMIN D 20,000 IU PER WEEK FOR FIVE YEARS DOES NOT PREVENT PROGRESSION FROM PREDIABETES TO DIABETES. JCEM 2016

Comparison of Study Design

	Tromso study	D2d	
Cohort	"Convenience"	New	✓
Eligibility - Age	25-80	>25	
Eligibility - Glycemia	FPG, 108 - 124 and/or 2hPG 140 - 198 (All had A1c 5.8 - 6.9)	2-out-of-3 (FPG, 2hPG, A1c)	✓
Intervention	D_3, 20,000 IU weekly (~2,900 daily)	D_3, 4000 IU daily	✓
Extra-study vitamin D	< 400 IU/daily	< 1000 IU/daily	
Outcome Assessment	Yearly	Semi-annually	✓
Outcome definition: Incident Diabetes	FPG or 2hPG (or A1c; added in 2012) or diabetes outside of study	2-out-of-3 or confirmation (FPG, 2hPG, A1c), or diabetes outside of study [adjudicated]	✓
Sample size & assumptions	Incidence, 10% per year Risk reduction, 30% Dropout, 20% per year N=505	Incidence, 10% per year Risk reduction, 25% Dropout, 5% per year N=2,382	✓

"Our power calculation was obviously too optimistic and a larger study might have disclosed statistically significant differences."
Jorde et al

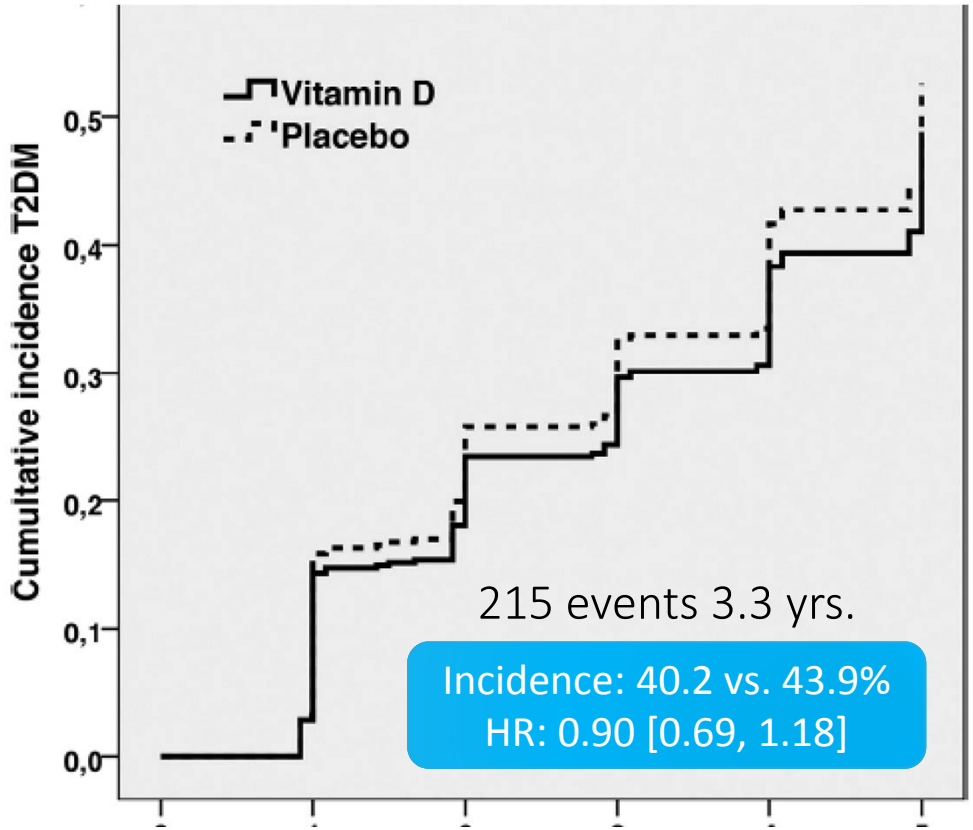
Baseline Characteristics

	Tromso	D2d	
Age	62	59	
Women, %	40	49	
White race, %	100	64	✓
Body mass index, kg/m^2	30	32	✓
Vitamin D supplement use, %	90	19	✓
Fasting plasma glucose, mg/dL	110	108	
2h plasma glucose, mg/dL	132	137	
A1c, %	5.98	5.91	

✓ Nearly Identical Population
in relation to glycemic profile at baseline

Incidence of diabetes, vitamin D vs. placebo

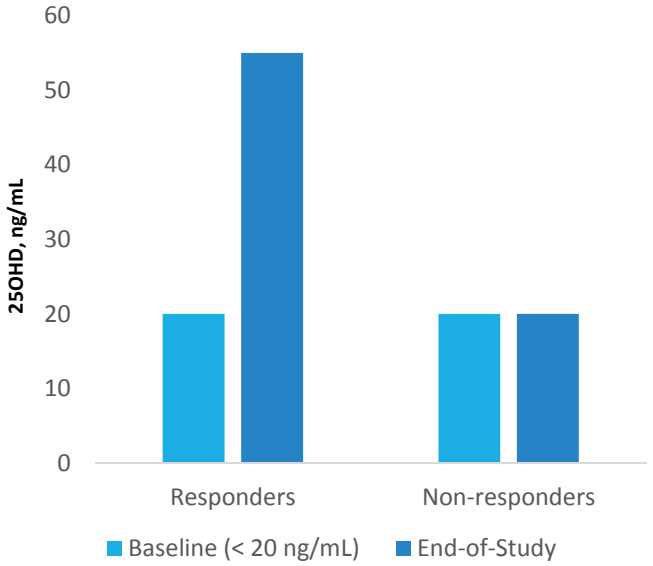
Every measure of glucose metabolism and insulin resistance were better in the vitamin D than the placebo.

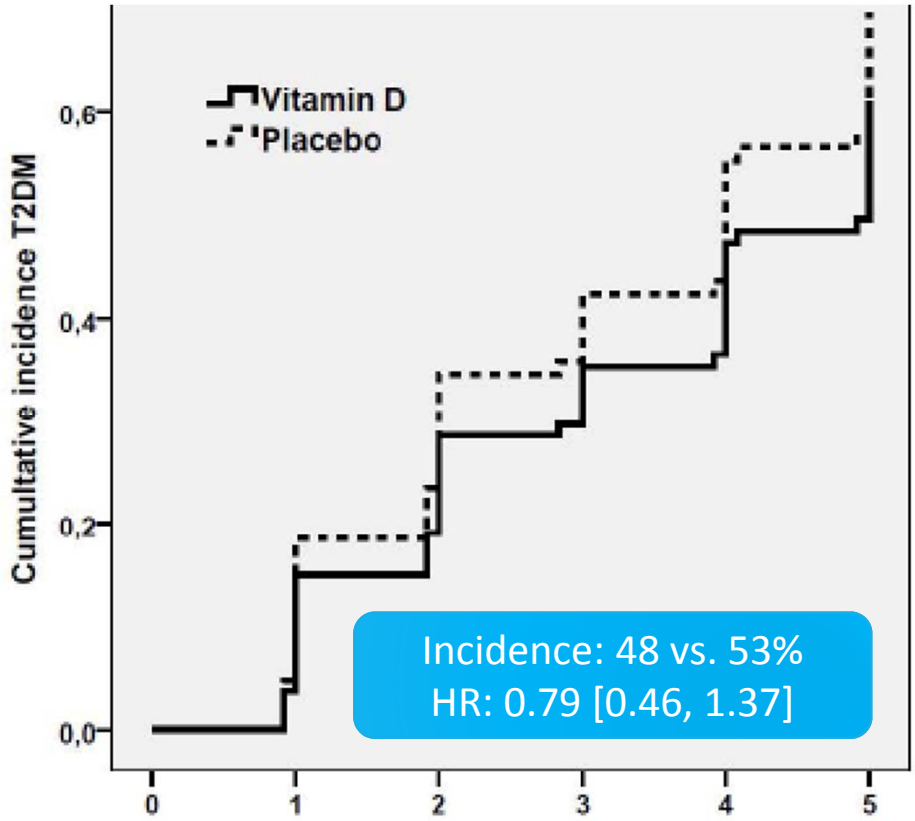


Jorde et al JCEM 2016

Incidence of diabetes, vitamin D vs. placebo

Among Those With Low Levels At Baseline, "Responders" (on Vitamin D, **N=63**) vs. "Non-responders" (on Placebo, **N=49**)





Jorde et al JCEM 2016

The Tromso study is good news for D2d

Re-assuring safety profile.

Underlying hypothesis remains very relevant and unanswered.

Equipoise is maintained, i.e. risk-benefit ratio is unchanged for D2d participants.

D2d study advantages

- ✓ Identical population *plus*
- ✓ Several advantages
  - Non-white participants
  - Daily and higher dose of vitamin D
  - Lower out-of-study vitamin D use
  - Rigorous diagnosis of diabetes
  - **Much larger sample size (~5x)**

What do we know about pre-diabetes?

"We can change the natural history of diabetes through routine screening to find pre-diabetes and early diabetes, combined with management aimed to keep glucose levels as close to normal as possible"

Phillips et al. We can change the natural history of diabetes.

Diabetes Care Oct 2014

"…debate about how well the new and expanded definitions of pre-diabetes are associated with future diabetes and arterial disease…

…no study has assessed the new lower ADA glycated hemoglobin threshold"

…we argue that current definitions risk unnecessary medicalization and create unsustainable burdens for health care systems.

Yudkin and Montori. The epidemic of pre-diabetes: the medicine and the politics.

BMJ July 2014

WE EXPECT D2d TO RECONCILE THESE OPPOSING STATEMENTS

D2d publications

1. Pittas et al. Rationale and Design of the Vitamin D and Type 2 Diabetes (D2d) Study; A Diabetes Prevention Trial. *Diabetes Care 2015*
2. Aroda et al. Optimizing use of the electronic health record (EHR) to identify persons at high risk of diabetes in the D2d study. *ADA 2016 (poster).* Manuscript in preparation
3. Vogel et al …Facebook as a recruitment tool for clinical trials: The D2d Study experience *NIH student conference (poster)*
4. Lewis et al. Management of Hemoglobin Variants Detected Incidentally in HbA1c Testing: A Common Ethical Problem currently Lacking a Standard Approach. Provisionally accepted to Diabetes Care
5. DeSouza et al. Baseline characteristics that predict pre-diabetes eligibility in the D2d study. In preparation
6. Brodsky et al. Reclassification of patients with prediabetes upon repeated testing. In preparation

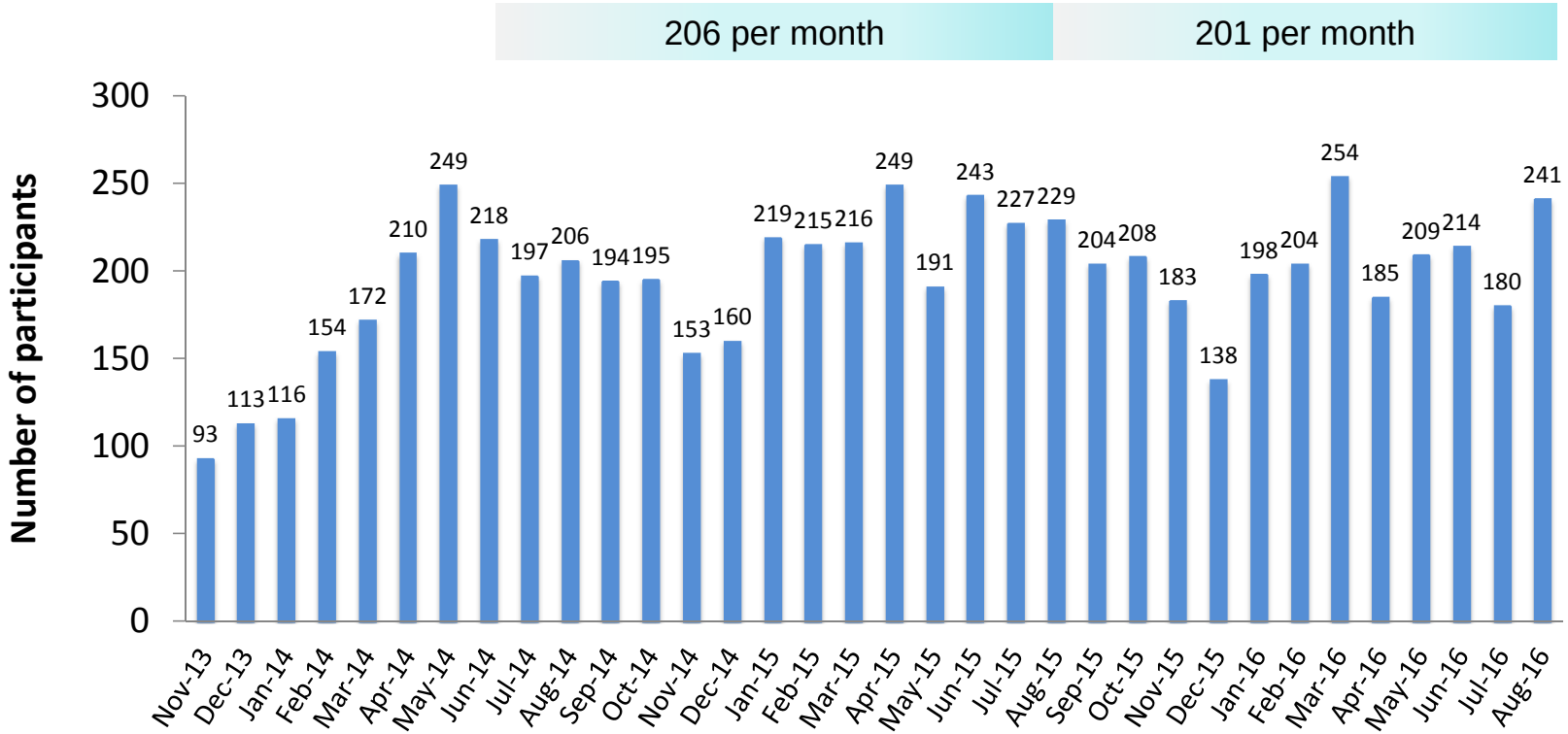

FUTURE
D2d

How is D2d doing?

DATA AS OF AUGUST 31, 2016


RECRUITMENT

Screenings


206 per month
201 per month
Number of participants
300
250
200
150
100
50
0
93
113
116
154
172
210
249
218
197
206
194
195
153
160
219
215
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191
243
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229
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138
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254
185
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214
180
241
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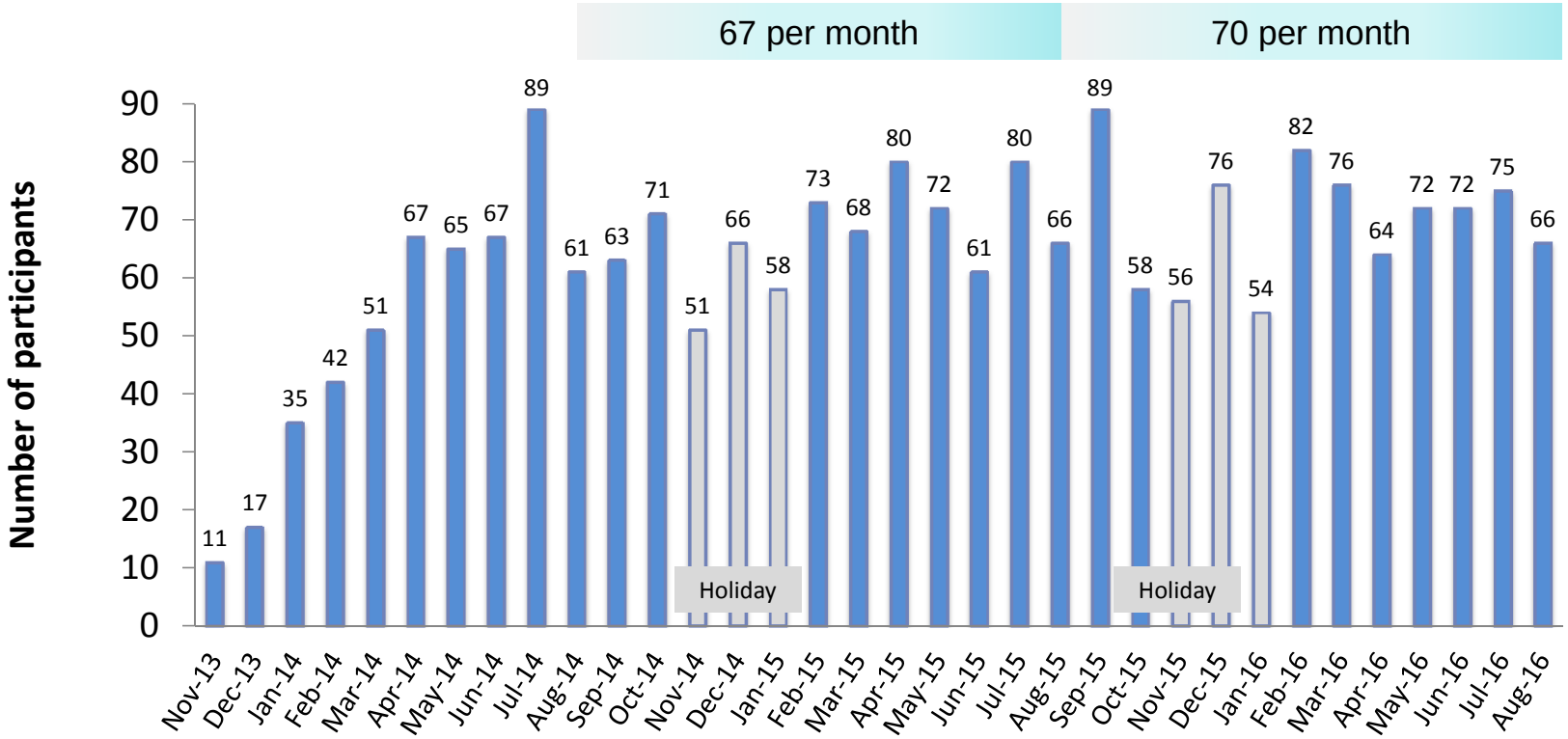
Aug-16

Randomized


67 per month
70 per month
Number of participants
90
80
70
60
50
40
30
20
10
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11
17
35
42
51
67
65
67
89
61
63
71
51
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68
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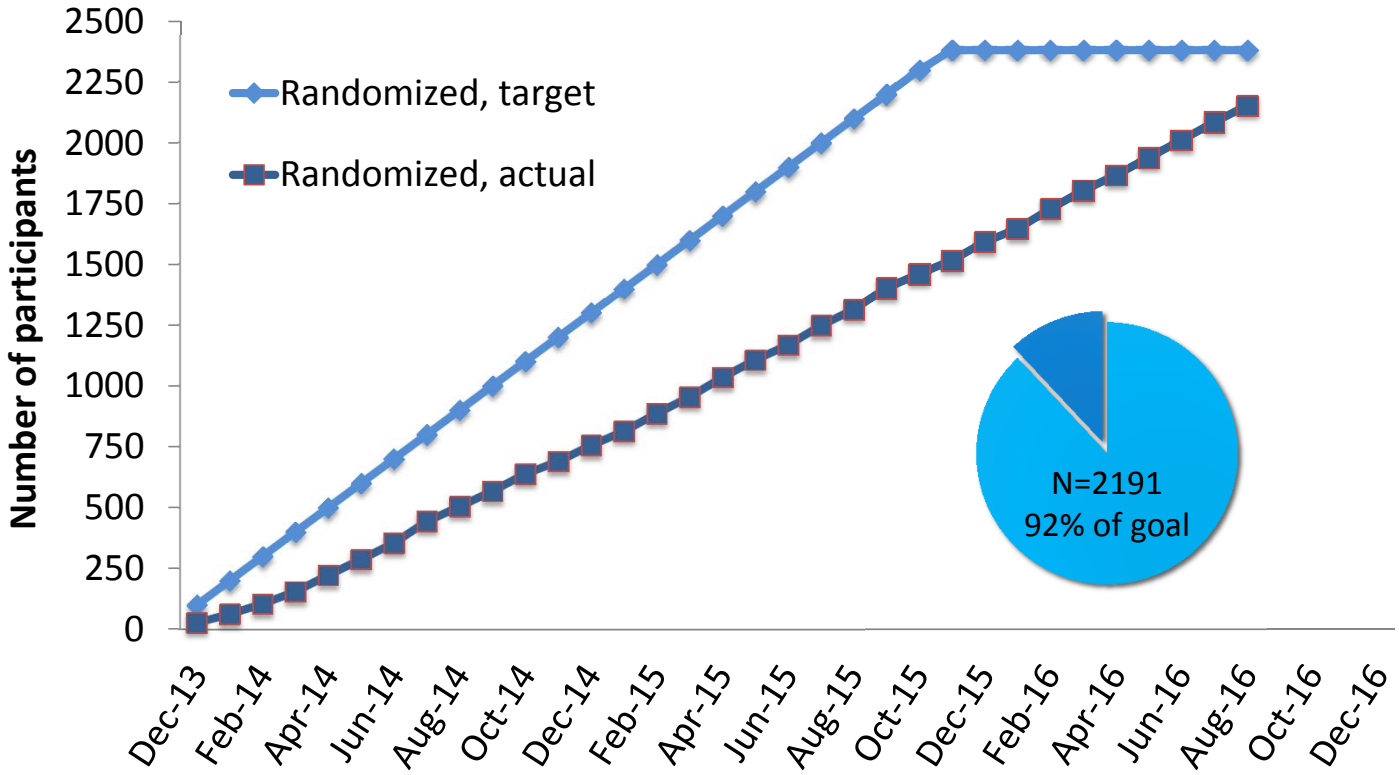
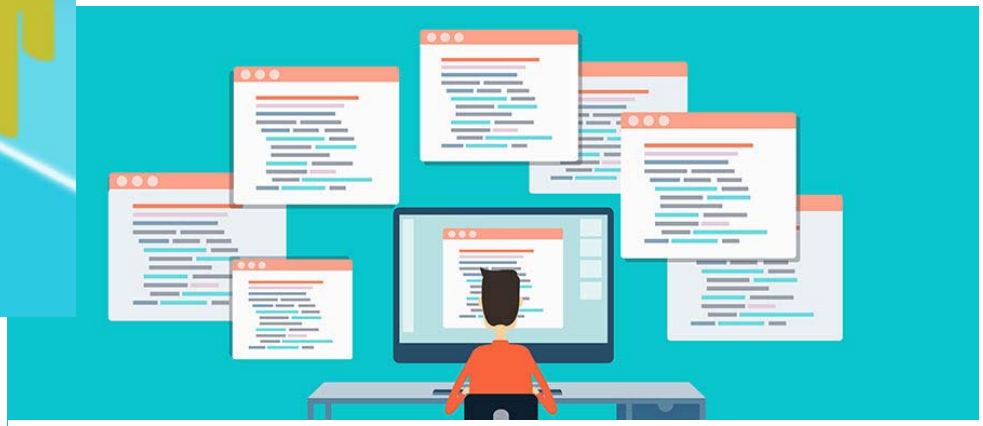
Cumulative randomization



Recruitment is a roller-coaster

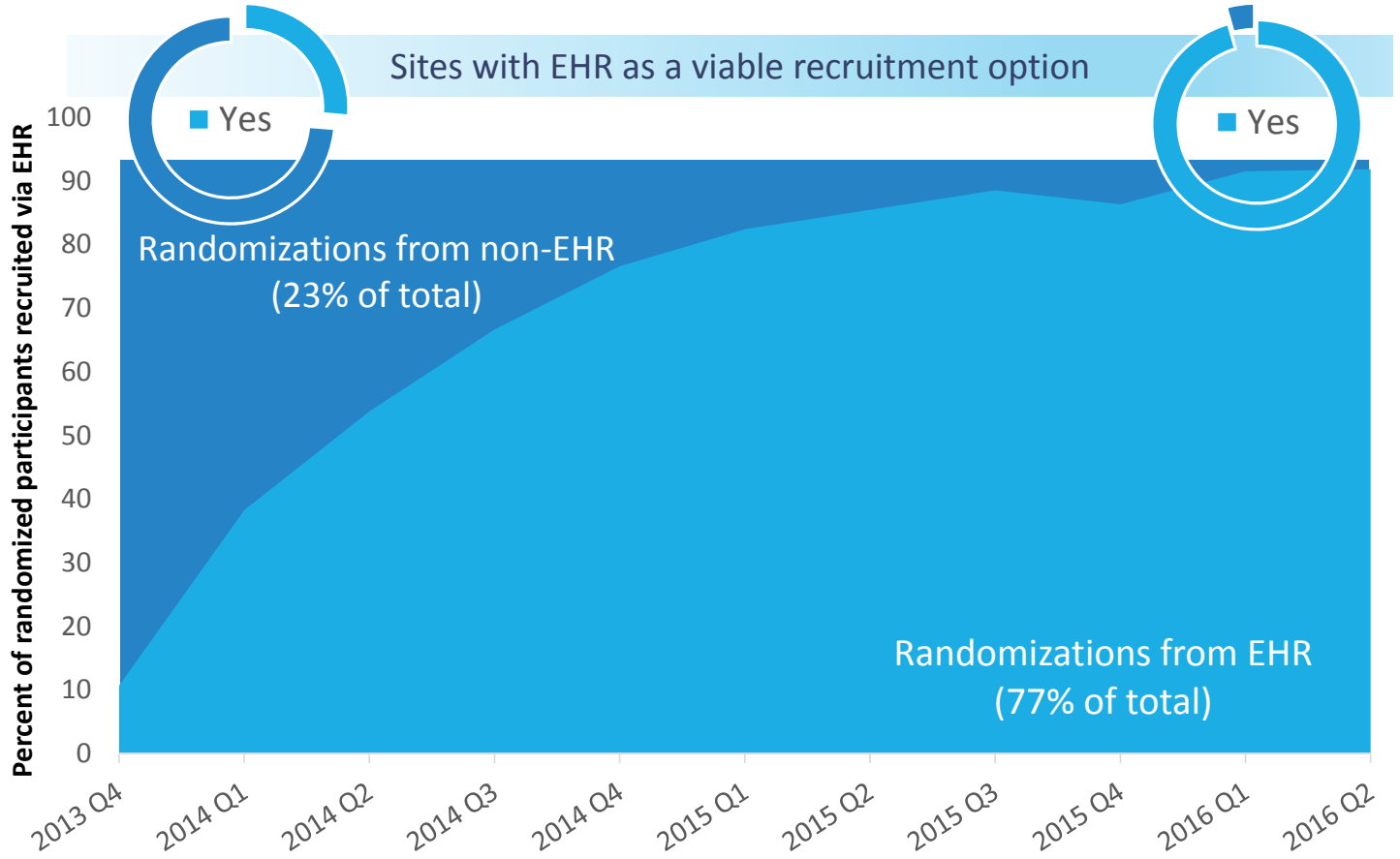
Recruitment via Electronic Health Records

More like this

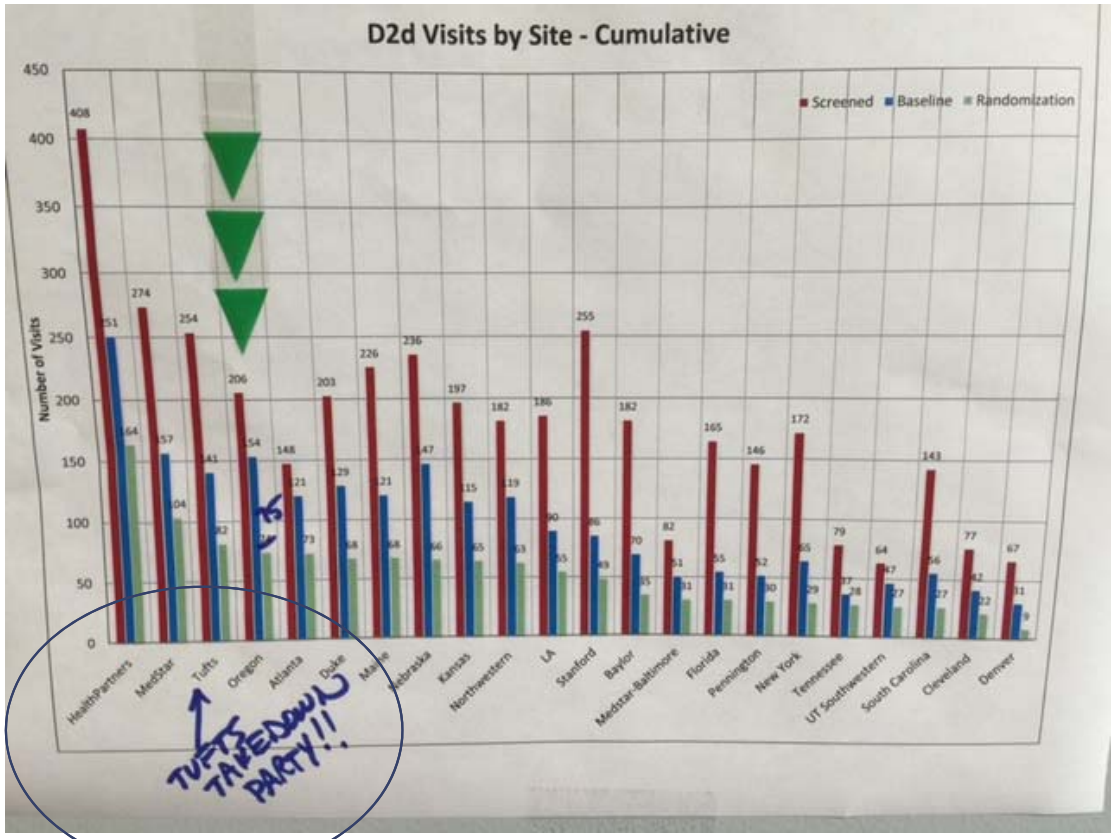


Is it worth it?

Effect of EHR on recruitment



Site Pride & Good-Natured Competition



Site Pride and Good-Natured Competition

From: Newcomb, Jefferey A [mailto:jeff.newcomb@unmc.edu]
Sent: Wednesday, August 03, 2016 12:04 PM
To: Vickery, Ellen; Pracht, Shelby; Rodriguez, M Grace; 'ramesh.ramalingam@va.gov'; Asgarpoor, Tara A; Eggert, Jenna T; Tillson, Renee L; Desouza, Cyrus V; Sheehan, Patricia
Subject: RE: Nebraska weekly reports - D2d **monthly report attached

My job here is done...we have OFFICALLY accomplished the "impossible" and caught Tufts in my 6 month promise. I'm thinking of pulling a Payton Manning and just retiring right now while on top (football reference).....however.....we could go for MedStar next! :) They better watch their backs...if they don't pick up the pace we are going to take over third place before this study ends! Looks like Nebraska corn fuels more than just our cars...it gets the Nebraska crew going as well! LOL Congrats Nebraska D2d Team on the monster accomplishment!!!!!!!!

Jeff Newcomb
VA/UNMC Research Coordinator
402-995-3924

A good D2d day is a good day!

FW: D2d participant 020017 study result

TI

Tam, Idy
Thursday, February 4, 2016 at 12:15 PM
To: Pittas, Anastassios

You replied to this message on 2/4/16, 12:40 PM.

Exciting day today. 1 diabetes outcome and 3 out of 3 baselines eligible!

-Idy

From: Rave@mdsol.com [Rave@mdsol.com]
Sent: Thursday, February 04, 2016 11:57 AM
To: Pittas, Anastassios; Casey, Erin; Tam, Idy; Vo, Kim T; Gefell, Lindsay; D2D
Subject: D2d participant 020017 study result

D2d participant 020017 had a positive fasting plasma glucose (GLU0) at Unscheduled-Confirmatory Visit visit collected on 29 Jan 2016.
Please follow algorithm in protocol and MOP18 for next steps

"When will recruitment end and how?"

"When will recruitment end and how?"

1. Active recruitment (i.e., no letters/no calls) stops when [based on the weekly report] current RAN + awaiting RAN **= 2,382.**
2. The CC will email sites when active recruitment stops.
3. Scheduled SCR and BAS visits are allowed to proceed.
4. It is up to the sites to schedule SCR visits for people who qualify after pre-screening phase and really want to be in D2d.

Steps 3 and 4 will result in a total RAN of **~2,410**

Study Conduct

Protocol deviations

No major protocol deviation since last year

Retention

Non-retention

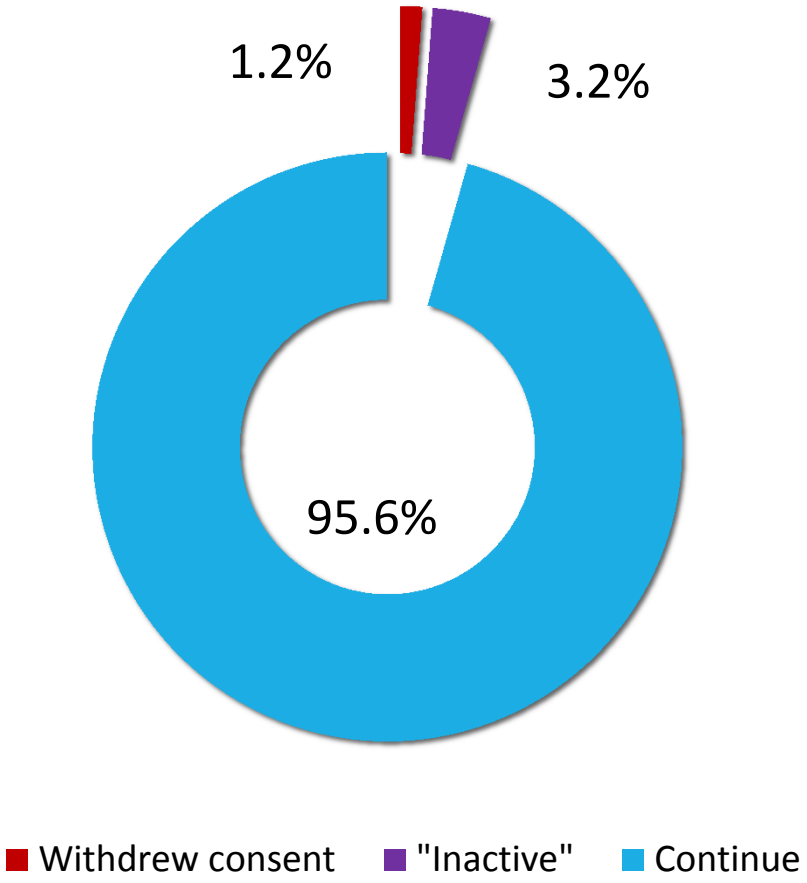
- Withdrawal of consent

Inactive

- Missed 2 consecutive visits, but not withdrawn

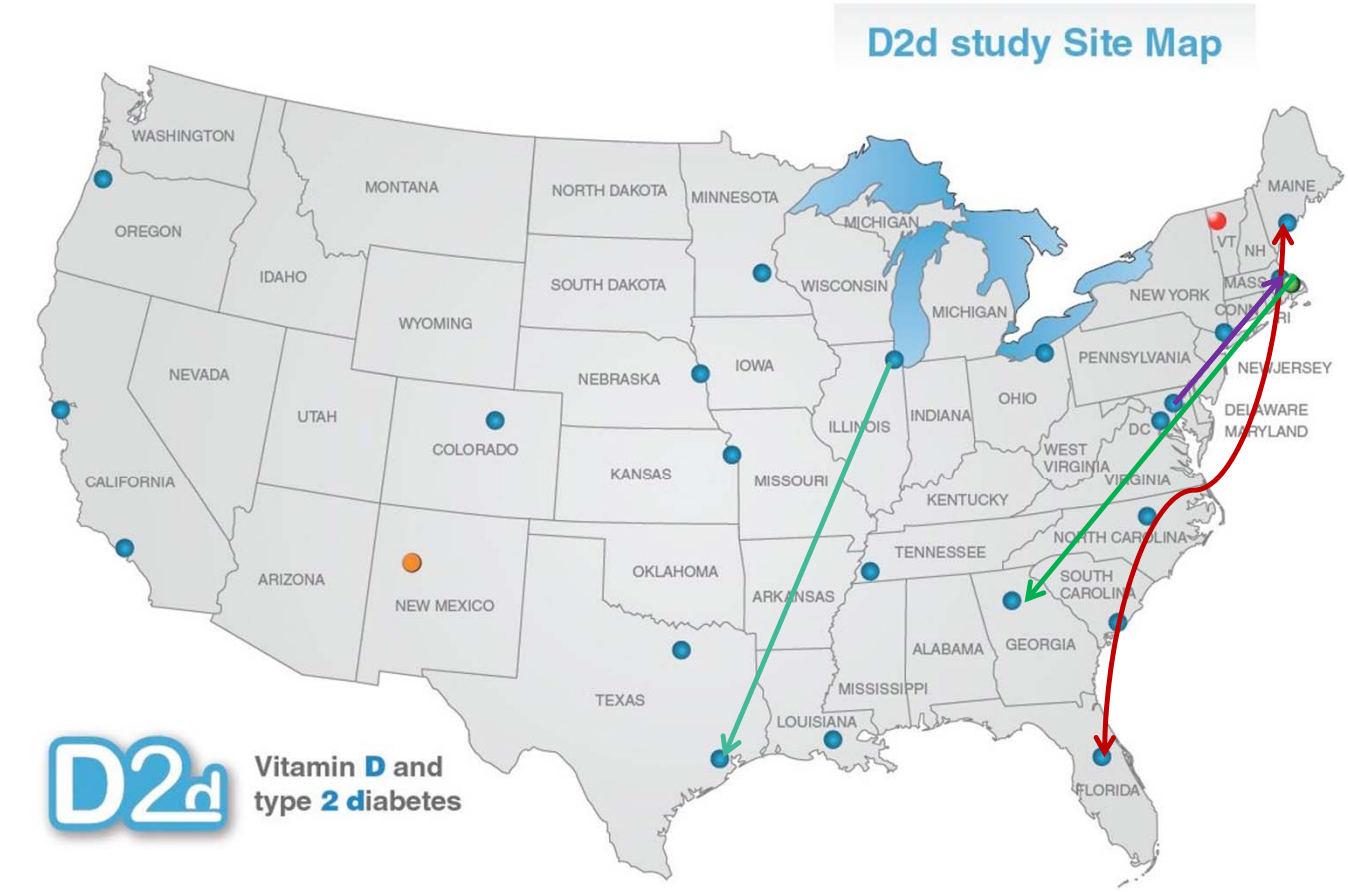
Lost-to-follow-up

- Defined at end of study



D2d site hopping

A fun way for participants to stay in D2d



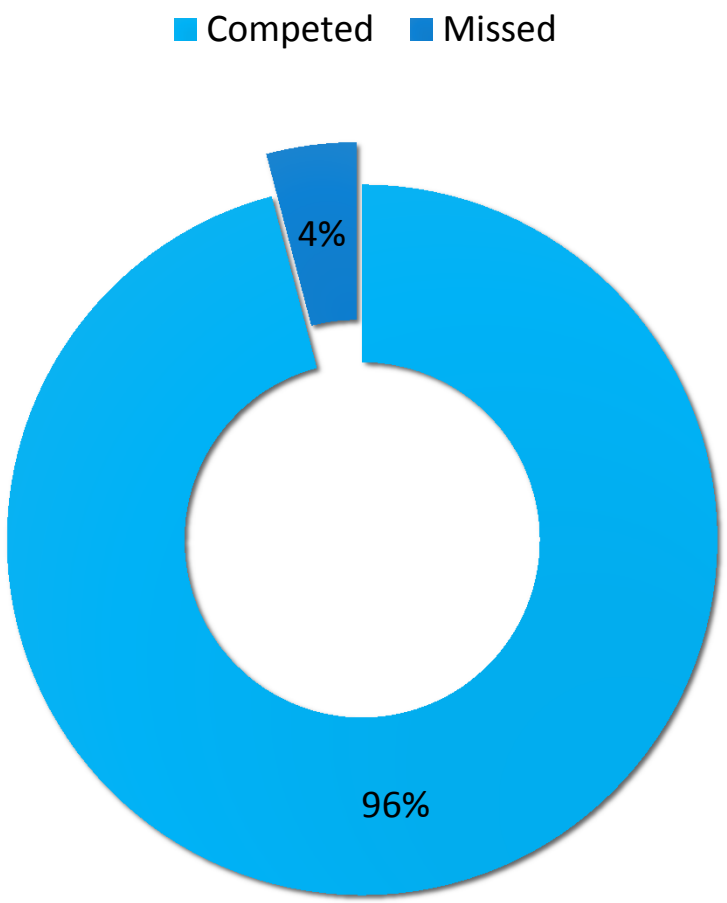
Maine to Florida (Shared)

MedStar-Baltimore to Tufts (Transfer)

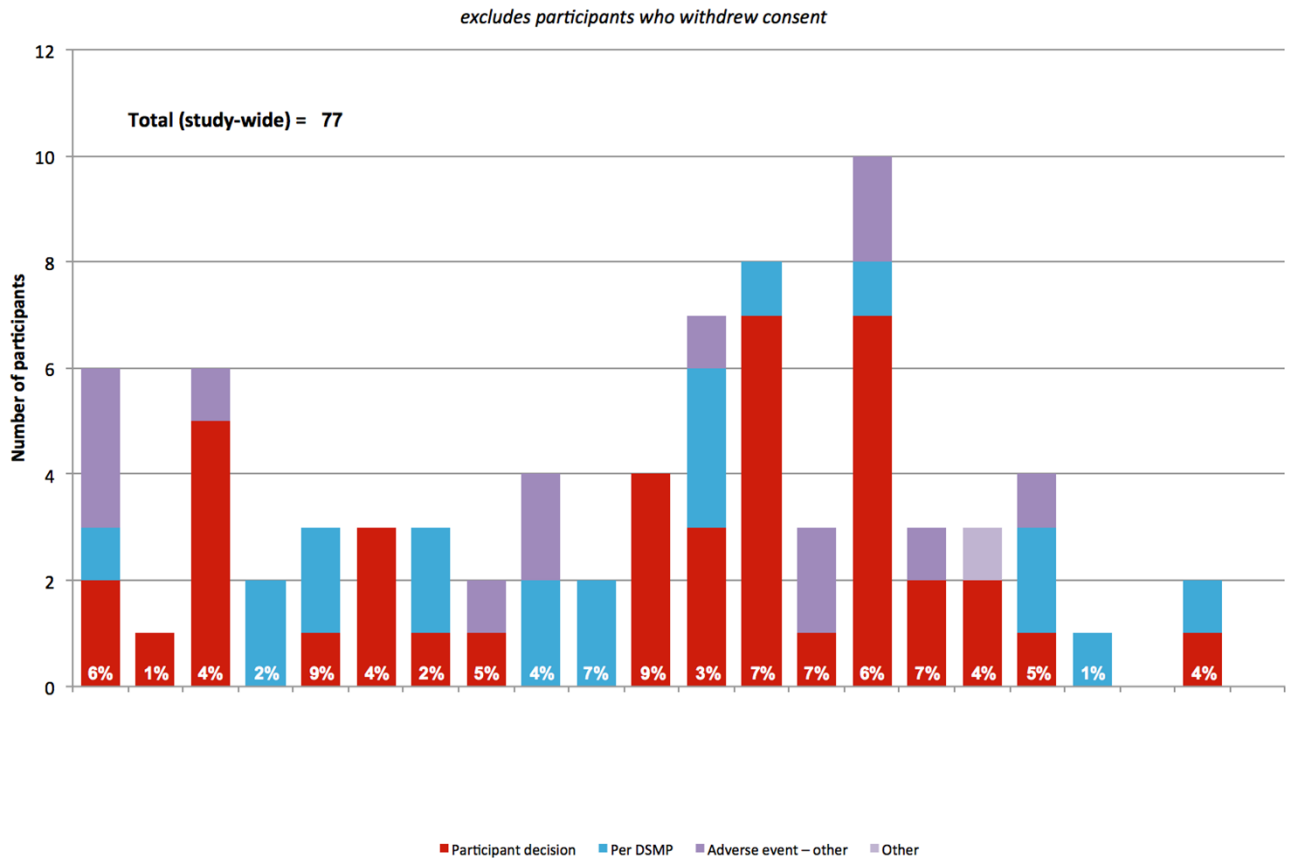
Tufts to Atlanta (Transfer)

Northwestern to Baylor (Transfer)

Scheduled Encounters



Off study medication



Baseline Characteristics

Age, Gender, Race, Ethnicity

Age, mean, years	59
Women, %	45
Race, %	
American-Indian / Alaska Native	0.5
Asian	5.2
Native Hawaiian or Other Pacific Islander	0.2
Black or African American	26
White	66
Other	2
Ethnicity, % Hispanic or Latino	10

Weight, Blood Pressure and Glycemia [mean]

Body mass index, kg/m^2	32.0
Waist circumference, cm	104.9
Systolic blood pressure, mmHg	128.3
Diastolic blood pressure, mmHg	76.9
Vitamin D intake, units/day	306
Fasting plasma glucose, mg/dL	107.7
2h plasma glucose, mg/dL	137.3
A1c, %	5.91

Categories of Pre-diabetes at baseline, % total

Met all 3 criteria	**33**
Met FPG and A1c	**49**
Met FPG and 2h Glucose	7
Met A1c and 2h Glucose	11

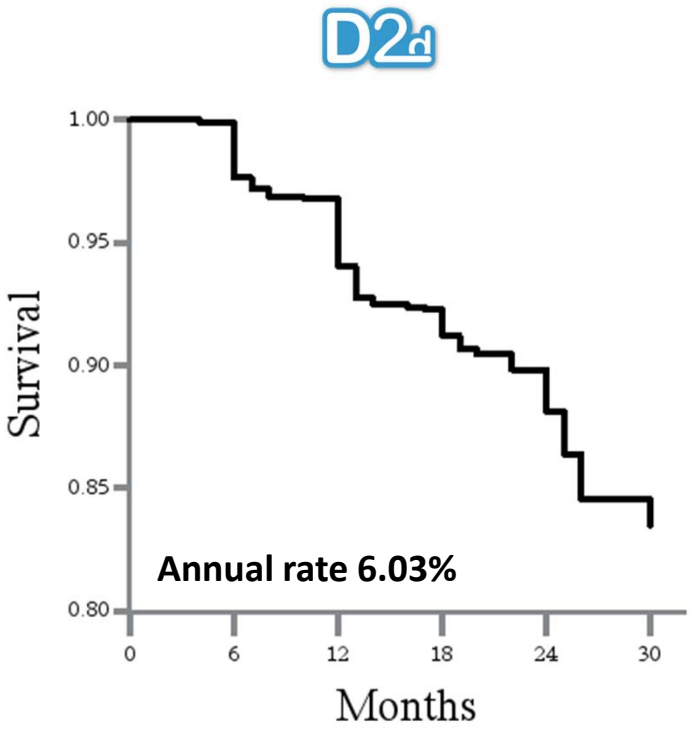
Met 2h Glucose	**51**

Safety

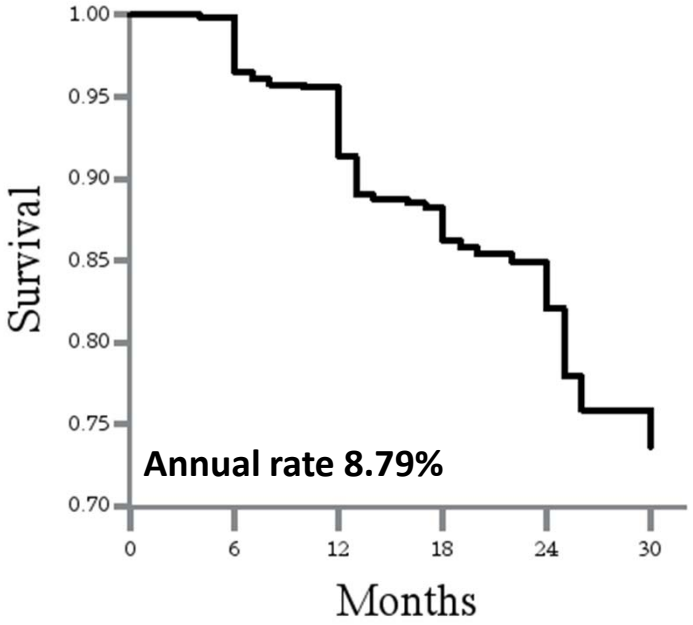
STAY TUNED FOR LAWRENCE PHILLIPS, MD

Outcomes

Diabetes-free Survival (Kaplan-Meier curve)



D2d – DPP like*



* Among D2d participants meeting DPP eligibility criteria (FPG 95-125; 2hPG 140-199 mg/dl)

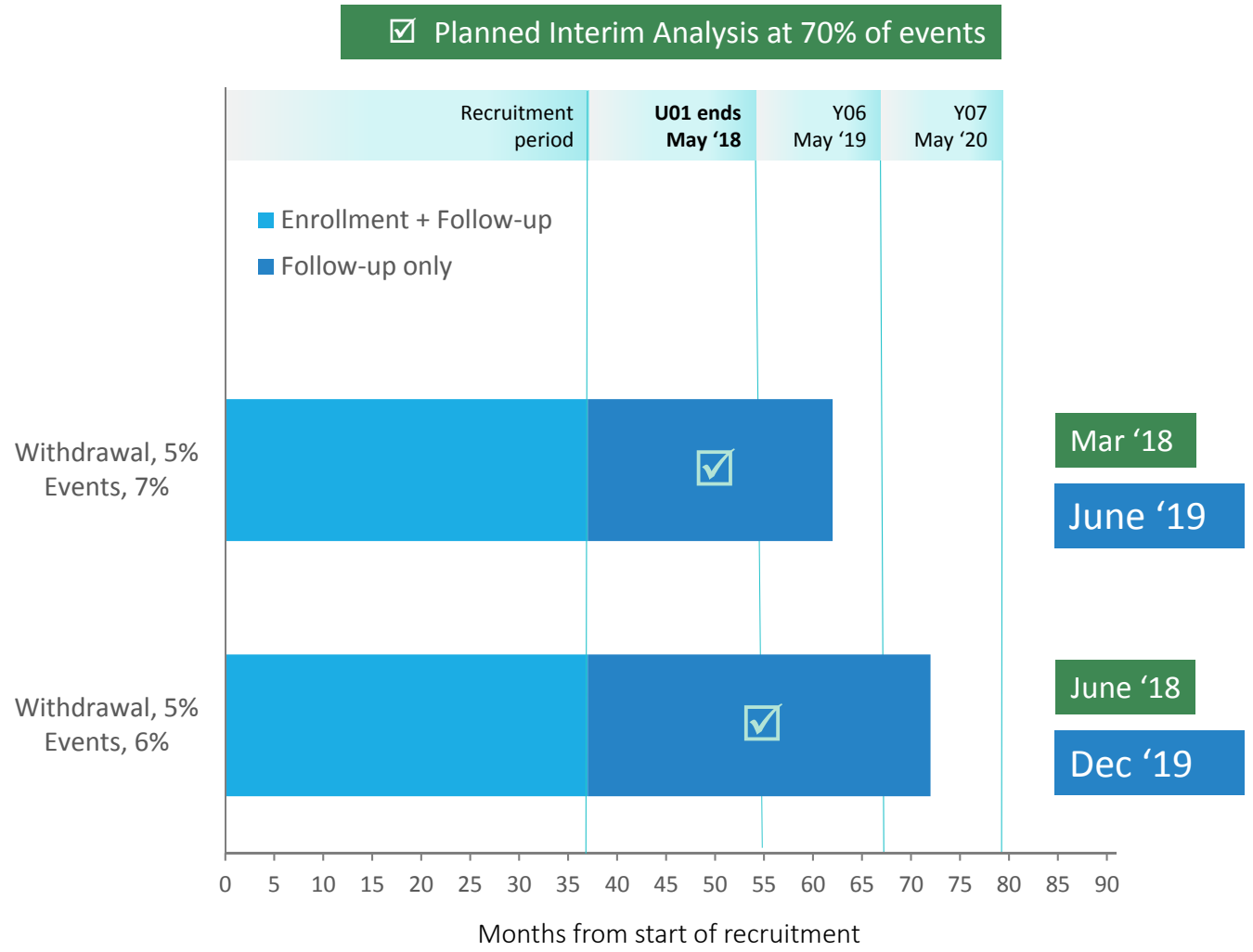
Projections

TIME TO REACH REQUIRED NUMBER OF EVENTS

Projections

To reach number of events

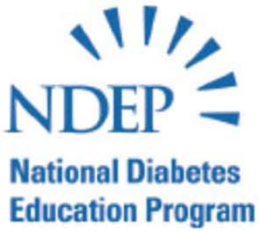
Randomized	**2,382**
Events needed	**508**
Accrual (monthly)	66
Withdrawal rate (annual)	5%
Event rate (annual)	6%



Primary Sponsor

National Institute of Diabetes and Digestive and Kidney Diseases

Other Sponsors



Exec Committee (aka D2d *support* group)

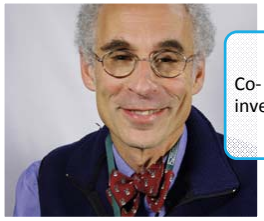
Taso Pittas, MD MS

Principal Investigator

Bess Dawson-Hughes, MD

Co-Investigator

Cliff Rosen, MD



Co-investigator

Patty Sheehan, RN, MPH, MS

Project Manager

Dave Reboussin, PhD

Lead Statistician

David Robbins, MD

Co-Investigator

Myrlene Staten, MD

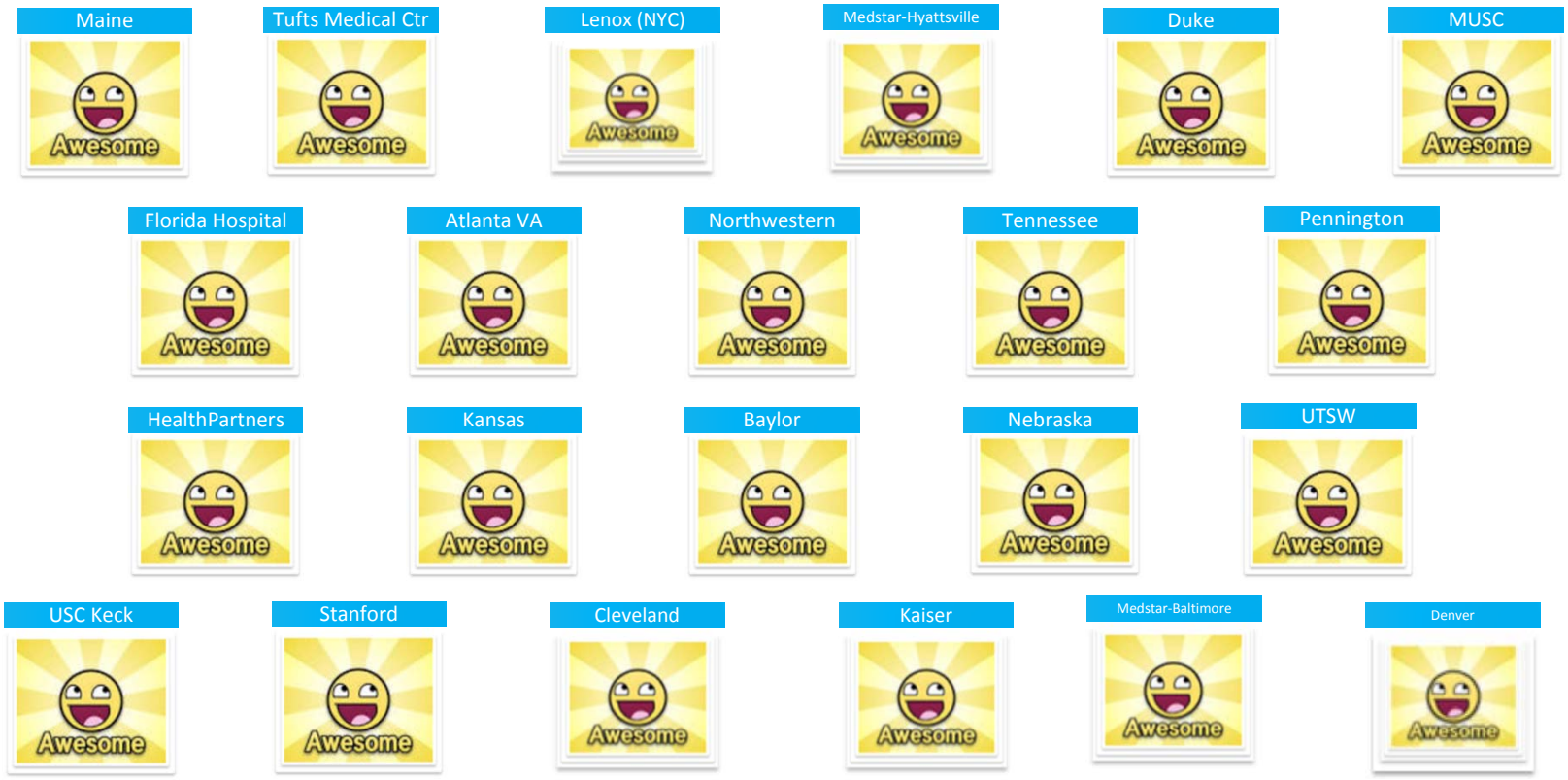
NIDDK Project Scientist

Saul Malozowski, MD

NIDDK Program Official

Central Laboratory

Collaborating Clinical Sites
The D2d Dream Team



Coordinating Center

Patty Sheehan, RN, MPH, MS

Project Manager

Paul Fuss

Research Associate

Ellen Vickery, MS

Data Manager

Cindy Haviet

Research Assistant

Olivia Lovegreen

Research Administrator

Danielle Riggs

Director, Research Administration

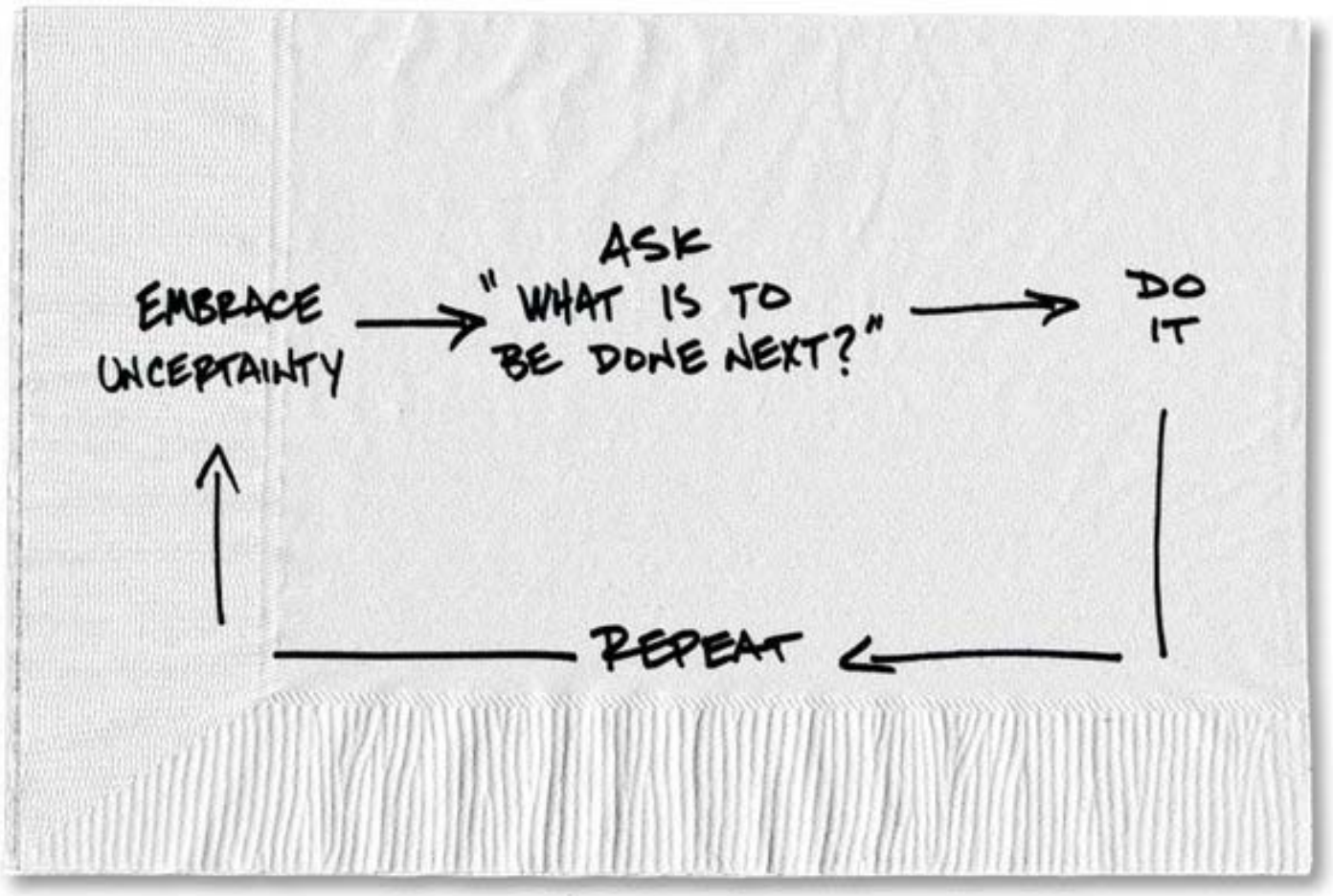
Jason Nelson, MPH

Analyst

Dave Reboussing, PhD

Lead Statistician

What is the secret to D2d ?




Northwestern
Medicine
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